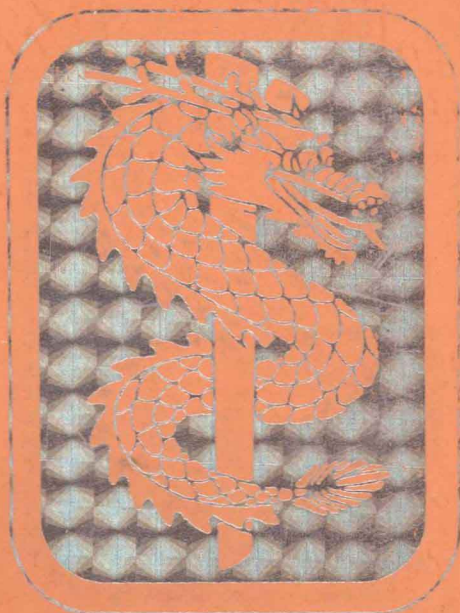


中国病毒性肝炎防治学术研讨会
论文集

Symposium on the Control of Viral
Hepatitis in China



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中国病毒性肝炎防治学术研讨会论文集
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主编 中国协和医科大学 CMB 病
毒性肝炎项目管理委员会

一九九六年十月 · 杭州

序

中国是病毒性肝炎流行严重的国家之一。1992 年美国中华医学基金会(CMB)主席 William D. Sawyer 博士在我们一次交谈中谈到中国肝炎的现状。作为一名著名的微生物学家,深知病毒性肝炎对人民健康的危害。他提出 CMB 可设立一个病毒性肝炎的研究项目,中国协和医科大学、上海医科大学、北京医科大学、中山医科大学和华西医科大学联合起来,针对中国的实际情况,研究病毒性肝炎的防治对策,并建议我负责这项研究的组织工作。于是,1992 年 4 月在北京召开了一次座谈会,同年 5 月 1 日又在北京召开了“中国肝炎防治战略研讨会”。(The strategy of the control of viral hepatitis in China)。上述五所医科大学肝炎方面的主要研究人员分别报告了当前中国以及世界对甲、乙、丙、戊型肝炎的研究现状和存在的问题。同时讨论了“中国病毒性肝炎防治战略”的研究方案。Sawyer 博士对方案作了重要和具体的建议。在此期间,J. L. Melnick 及 William S. Robinson 教授对方案作了认真的审查。1993 年 5 月,CMB 批准了这个方案并决定给予经费资助。

自 1993 年 5 月到现在,巴德年校长全面领导下,已经开展了三年。这个项目共有四个课题,十一个子课题,约 130 人参加。三年来对甲型肝炎减毒活疫苗的效果、残留毒力返祖可能性、乙型肝炎疫苗的人群防治及新生儿免疫失败的原因、丙型肝炎及戊型肝炎的流行病学以及分子生物学作了研究,同时还研究了丙型肝炎与肝癌的关系以及治疗乙型肝炎新药—双环醇。

这次会议是为了总结三年多来的科研工作进展,探讨今后二年的工作,希望在过去工作的基础上取得有价值的成果,向中国卫生行政部门提出防治病毒性肝炎的建议,为控制中国的肝炎作出贡献。

这本论文集汇集了这次讨论会的所有报告,过去已发表的论文,则只列出题目,为大家参考。

这次会议我们还邀请了一些知名的病毒性肝炎专家,他们的学术报告也一并收在本论文集中。在此向他们表示衷心感谢。

顾方舟

1996 年 7 月 25 日

PREFACE

Viral hepatitis is a major medical problem worldwide, and causes acute and chronic liver diseases, even liver cirrhosis and hepatocellular carcinoma, and is one of leading causes of death. China is one of countries of high endemicity for viral hepatitis infection. As a distinguished microbiologist, Dr. William D. Sawyer, president of China Medical Board (CMB), is deeply concerned about the harmfulness of viral hepatitis to health of the people. In 1992, Dr. Sawyer had a friendly conversation on a subject relative to the research and control of hepatitis virus infection of China with me, and expressed that CMB will attempt to support a program of viral hepatitis for solving this actual medical problem in China. Then he proposed that collaboration between Peking Union Medical College, Shanghai Medical University, Beijing Medical University, Sun Yi Sian Medical University and China West Medical University will be required to study the strategy of prevention and therapy of viral hepatitis of China, and suggested the program be organized by me. Thus, a communication meeting was called by Peking Union Medical College in April, and a Workshop on The Strategy of the Control of Viral Hepatitis in China was held on May First, 1992. On this workshop, the principal investigators, engaged in speciality of viral hepatitis, from the five universities gave presentations of the current progress and the existing problems in the studies related to hepatitis A, B, C and E, and discussed the proposal about the program. Dr. Sawyer contributed the valuable ideas and offered important suggestions in very concrete items relative to the proposal. Professor Joseph L. Melnick and professor William S. Robinson carefully reviewed the proposal during the workshop. In May 1993, CMB approved the protocol of the viral hepatitis program and decided to give financial support.

The viral hepatitis program has been implemented over three years from July 1993. This program consists of four research projects involving eleven subprojects. Totally about 130 professors, researchers and other professionals, organized by the principal investigators of the research projects, are working together for achieving the objectives of the program. Since 1993 the wide range of scientific studies on viral hepatitis have been conducted as follows: evaluation of effectiveness of attenuated live hepatitis A vaccine; study on possibility of virulence reversion of attenuated live hepatitis A vaccine strain; community – based hepatitis B prevention; study on cause of failure with hepatitis B vaccine in infants of carrier mothers; study on epidemiology of hepatitis C and E; study on molecular biology of hepatitis B and C virus; study on relationship between hepatitis C and liver cancer; clinical and basic study on a new antiviral hepatitis B drug – Bicyclol.

The theme of this meeting is to exchange the new development and achievements in the studies mentioned above, and to discuss the problems relative to the research projects next two years. It is expected that more valuable achievements will be obtained in the future, based on the studies carried out in the last three years, and that the relative scientific evidences will be submitted to the Ministry of Public Health of China for making decision in the prevention and therapy of viral hepatitis. It is hoped that greater contribu-

tions, in the implementation of the CMB hepatitis virus program, will be made in a common effort to the control of viral hepatitis of China.

The proceedings contains all the papers relative to the CMB hepatitis virus program submitted to the conference organized by the scientific committee of the program, and covers the titles of the published papers supported by the CMB program.

It is hoped that this proceedings would be of great interest to those responsible for the research of viral hepatitis and for medical care of patients suffering from viral hepatitis.

A handwritten signature in black ink, reading 'Gu Fungzhou' in a cursive style.

Gu Fungzhou M.D., Ph.D., FRCP

July 25, 1996

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Title of article/publication

血源性乙型肝炎表面抗原疫苗免疫后九年的前瞻性队列研究

刘崇柏^① 曹惠霖^① 徐志一^② 夏国良^①

摘要 为了评价血源性乙型肝炎表面抗原疫苗免疫后的长期效果,1946名于1986—1988年新生儿期接受了不同剂量的HBsAg血源性疫苗者做为观察人群,用放射免疫法筛检此出生年龄段的免疫儿血清HBsAg、抗-HBs、抗-HBc、剔除HBsAg或抗-HBc阳性儿,选取不同抗-HBs滴度的阳性儿做为观察对象。将对象又分为出生于HBsAg携带母亲的儿童和HBsAg阴性母亲两个组,互为对照进行前瞻性观察。并每年采血一次用RIA进行HBsAg、抗-HBc和抗-HBsHBV血清指征的检测。

免疫方法为0、1、6月。HBsAg携带者母亲的儿童接受以下几种免疫方案:20 μ g/ml $\times$ 3,20 μ g/ml,10、10、30 μ g/ml,10、10,三种剂量程式。出生于健康母亲的新生儿均接受10 μ g/ml3针,免疫程式。

结 果

在研究期内共观察1946名免疫儿童共12059人、年,17名儿童再感染后出现HBsAg无症状病毒血症,除2名外,都成为HBsAg无症状携带者,所有出现HBsAg血症的儿童均无抗-HBs免疫回忆反应。(表1,2),76%的HBsAg携带者为出生于HBsAg阳性母亲的儿童。这些儿童中再感染主要发生在2~3岁(71%,10/14),而出生于HBsAg阴性母亲的儿童,HBsAg血症多发生在5~6岁(表2)。HBsAg携带者母亲的儿童,HBsAg病原血症阳性率为0.36%/人、年,HBsAg阴性母亲的儿童为0.036%/人、年,两者的相对危险度为10。(表3)

为什么HBsAg携带者母亲的儿童免疫后在2~3岁有一个/阳转(HBsAg)高峰,其机理还不清楚,这对于在乙型肝炎高流行区如何有效阻断母婴围产期传播以及如何正确实施加强免疫的策略提出了一个重要问题,实验仍在进行中。

Table 1 Case analysis of HBsAg converted children born to HBsAg carrier mother

code No.	years after vaccination	HBsAg S/N	HBsAb S/N	HBcAb Co/s	code No.	years after vaccination	HBsAg S/N	HBsAb S/N	HBcAb Co/s
hn11	1	—	18.3	4.7	hn43	1	—	15.2	—
	2	—	5.7	6.9		2	—	—	—
	3	21.8	—	6.1		3	28.5	—	2.1
	5	19.2	—	5.7		5	17.8	—	1.3
	6	11.3	—	9.3		6	27.6	—	—
	7	—	—	—		7	33.9	—	—
hn52	1	—	17.5	—	hn63	1	—	13.1	—
	2	—	5.2	—		2	12.5	—	—
	3	18.5	—	2.4		3	20.8	—	—
	5	14.7	—	—		5	17.4	—	2.7
	6	21.3	—	3.7		6	21.7	—	4.7
	7	17.1	—	4.1		7	36.6	—	5.8
hn72	1	—	11.2	—	hn86	1	—	32.5	—
	2	17.5	—	1.9		2	—	9.5	—
	3	20.5	—	2.7		3	10.0	—	2.1
	5	15.7	—	2.9		5	12.7	—	2.3
	6	12.9	—	—		6	17.6	—	—

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code No.	years after vaccination	HBsAg S/N	HBsAb S/N	HBcAb Co/s	code No.	years after vaccination	HBsAg S/N	HBsAb S/N	HBcAb Co/s
	7	10.5	—	2.3		7	12.0	—	2.4
gx24	1	—	56.5	—	gx28	1	—	11.5	—
	6	66.7	—	99.8		5	32.4	—	99.9
	7	50.1	—	83.1		6	12.1	—	99.0
	8	50.1	—	95.1		7	10.0	5.0	99.9
gx30	1	—	28.0	—	gd66	3	—	20.1	—
	3	43.6	—	99.9		4	—	53.7	—
	5	19.4	—	99.9		5	—	19.7	—
	6	11.7	—	90.5		7	15.8	—	2.3
sh4	1	—	—	—	sh47	1	—	—	—
	2	67.6	—	—		2	56.2	—	—
	3	10.0	—	—		3	23.0	—	—
	4	27.1	—	—		4	15.8	—	—
	5	20.0	—	—		5	—	—	—
zd	1	—	4.8	9.8	zj91	1	—	20.1	—
	2	63.5	—	70.0		6	21.3	—	2.0
	3	106.3	—	48.0		7	62.7	—	2.0
	4	93.6	—	39.7					
	5	108.0	—	18.0					
	6	42.1	—	19.2					
	9	51.2	—	10.4					

Table 2 Case analysis of HBsAg converted children born to HBsAg negative mother

code No.	years after vaccination	HBsAg S/N	HBsAb S/N	HBcAb Co/s	code No.	years after vaccination	HBsAg S/N	HBsAb S/N	HBcAb Co/s
zdw21	4	—	—	—	zd453	5	—	75.2	—
	5	58.7	—	—		7	—	30.0	—
	7	—	15.0	18.8		8	—	17.0	—
	8	—	7.9	11.5		9	75.6	—	12.9
	9	—	5.0	9.5		9	1:128	—	—
zdl434	5	—	77.6	—					
	7	—	19.1	—					
	9	21.4	—	—					
	9	1:128	—	—					

Table 3 Cohort study of children vaccinated by hepatitis B vaccine aged 1–10 years

subjects (1–10 years old children)	person – years observed	No. of HBsAg converted	conversion rate per 1000 person – years
born to HBsAg(+) mother	3805.5	14	3.68
born to HBsAg(–) mother	8253.0	3	0.36

Study on the Efficacy of Plasma Derived HBsAg Vaccine in Children – – A Nine Years Follow – up Study

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To evaluate the effectiveness of plasma derived HBsAg vaccine, 1946 children born to HBsAg carrier mothers, vaccinated 1986 – 1988, have been randomly selected for a long term efficacy cohort study from 1986 – 1995.

All of the subjects enrolled were both HBsAg and anti – HBc negative and at different level of anti – HBs positive, as prescreened by RIA at three month to one year after completion of the full doses vaccine injection.

Vaccination Schedule: $20\mu\text{g} \times 3$, $20\mu\text{g}$, 10, 10, or $30\mu\text{g}$, 10, 10, used for children born to HBsAg carrier mother and $10\mu\text{g} \times 3$ for other and a three injections of 0.1.6 month schedule have been adapted for all children, during the study time, blood sample were collected yearly for all volunteer children and detected for HBV infection markers by RIA.

During the study period, a total of 17 cases of volunteer children have converted to HBsAg antigenmia, and all of them became persistent asymptomatic chronic carriers, except two. There were no anti – HBs anamnestic reaction observed in the all HBsAg converted cases. (table 1, 2.). 76 % of the HBsAg cases were children born to HBsAg carrier mothers and the majority of them (71 % 10/14) occurred in 2 – 3 years old children, as compared with 5 – 6 years old children born to the healthy mothers. (table 2).

The average HBsAg conversion rate in children from HBsAg carrier mother was 0.368 % per person – year and 0.036 % per person – year in children from healthy mother.

The RR was more than 10. The mechanism of the early reinfection in children born to HBsAg mothers after relative high dose HBsAg vaccine immunization was unknown. It constitutes an important problem in HBV endemic area, such as China, effectively to prevent perinatal transmission as well as the establishment of right booster policy. The study is still undergoing.

几种治疗慢性乙型肝炎及重症 肝炎方案的研究

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摘要 1、慢性乙型肝炎的治疗 共 286 名肝活检证明的慢性活动性肝炎病例,分为 5 组:第一组为猪苓多糖合用乙肝疫苗(A 组),第二组为 LAK 细胞回输疗法(B 组),第三组为潘生丁合用卡介苗(C 组),第四组为干扰素组(D 组),第五组为对照组(E 组)。结果:血清 ALT 复常率 5 组分别为 64%、35%、57%、50%及 55%。HBsAg 阴转率分别为 5%、0%、0%、6%、和 0%。HBV DNA 阴转率分别为 44%、30%、61%、49%和 9%。HBeAg 阴转率分别为 43%、34%、57%、48%及 11%。抗-HBe 阳转率分别为 22%、21%、43%、36%及 17%。疗效机理研究:①用垂直传播感染鸭乙肝病毒(DHBV)阴性的麻鸭研究了猪苓多糖合用乙肝疫苗及卡介苗合用潘生丁对 DHBV 转阴的效果;②猪苓多糖、乙肝疫苗、潘生丁和卡介苗单独或联合应用对巨噬细胞吞噬功能和细胞溶解功能的影响;③猪苓多糖、乙肝疫苗和卡介苗体外对正常人外周单个核细胞(PBMC)杀伤活性的影响以及对 PBMC 细胞膜上 IL₂ 受体的表达及 IL₂ 分泌的影响;④慢性乙型肝炎病人 LAK 细胞治疗前后 LAK 细胞活性及血清 LAK 活性抑制因子对治疗效果的影响。

2、重症肝炎的治疗 病人共 165 名,分为 3 组。第一组为综合治疗合用促肝细胞生长素(PHGF)(A 组),第二组为综合治疗合用前列腺素 E₁(PGE₁)(B 组),第三组为综合治疗(C 组)。结果:重肝病人的病死率三组分别为 38.8%、37.6%及 65.8%。II⁰和 II⁰以上肝性脑病病人的病死率分别为 53.6%、47.1%及 79.3%。疗效机理的研究:①建立了急性肝坏死动物模型:用大肠杆菌内毒素和鸭乙肝病毒诱发鸭急性肝坏死(模型 A),应用 D-氨基丰乳糖和内毒素诱发小鼠急性肝坏死(模型 B),用丙酸杆菌和内毒素诱发小鼠肝坏死(模型 C);②用模型 A 研究了 PHGF 的疗效机理;③用模型 B 研究了 PGE₁ 和 PHGF 的疗效机理;④用模型 C 研究了 PGE₁ 的疗效机理;⑤用模型 A 研究了抗-TNF 单抗和肝细胞再生刺激因子(HSS)的治疗作用。

结论:①临床及实验材料均证明,4 种治疗方法对慢性乙型肝炎均有一定疗效;②临床和实验材料均证明,PHGF 和 PGE₁ 均能减少重症肝炎的病死率,对重症肝炎的治疗有一定的作用。

在 1985~1990 年多中心临床研究的基础上,选择了几种认为有效的治疗方法,于 1991 年~1995 年又进行了多中心的临床验证,同时也进行了有关疗效机理的研究,现将结果报告如下。

一、慢性肝炎部分

(一)临床验证及疗效考核 猪苓多糖合用乙肝疫苗组、LAK 细胞回输治疗组和潘生丁合用卡介苗组的疗效。见表 1、2、3。

Table 1 Therapeutic effect on SALT

group	total	normalization		lowering > 50 %		effective	
		No	(%)	No	(%)	No	(%)
A	78	50	(64) *	14	(18) *	64	(82) *
B	57	20	(35) #	14	(25)	34	(60)
C	23	15	(57)	5	(21)	18	(78)
D	64	32	(50) *	20	(31)	52	(81) # *
E	64	35	(55)	9	(14)	44	(69)

A: polysacchride of polypous umbellatus

B: LAK cell retransfusion

C: dipuridamole + HBV vaccine

D: interferon

E: control

compared with control $P < 0.05$

* cmpared with LAK $P < 0.05$

Table 2 Therapeutic effect on HBVM

group	total	HBsAg(-)(%)	HBVDNA(-)(%)	HBeAg(-)(%)	anti - HBe(+)(%)
A	78	4(5)	36(44) # *	34(43) #	17(22)
B	57	0	17(30) #	19(34) #	12(21)
C	23	0	14(61) # *	13(57) #	10(43)
D	64	4(6)	31(49) # *	30(48) #	23(36) #
E	64	0	6(9)	7(11)	11(17)

compared with control $P < 0.05$

* compared with LAK $P < 0.05$

Table 3 Therapeutic effect on HBVM after 1 year

group	total	HBsAg(-)(%)	HBVDNA(-)(%)	HBeAg(-)(%)	anti-HBe(+)(%)
A	78	4(5)	45(58) #	46(59) #	35(45) #
B	44	0	24(55) #	27(61) #	18(41)
C	20	1(5)	12(60) #	14(70) #	8(40) #
D	57	2(4)	30(52) #	31(54) #	24(42) #
E	54	0	4(7)	9(17)	6(11)

compared with control $P < 0.05$

经过上述多中心临床验证,猪苓多糖+乙肝疫苗组、LAK 细胞组、和潘生丁+卡介苗组经过一个疗程的治疗,在 HBV DNA 阴转率方面,三组疗效均优于对照组,提示对抑制 HBV 复制均有治疗作用。除 LAK 细胞组(疗程仅 1.5 个月)近期疗效较差外,猪苓多糖组和潘生丁组与干扰素组相似。而治疗结束 1 年时,上述三组疗效与干扰素组相似。

根据各组疗效,副作用及治疗费用综合评价,我们推荐对血清 ALT 升高和 HBsAg、HBV DNA 阳性的慢性乙型肝炎病人,首选猪苓多糖合用乙肝疫苗;对治疗效果不好病人亦可应用 LAK 细胞回输治疗;对上述治疗方法效果不好,经济困难的病人,如能严格治疗操作规程,取得病人合作,可以采用潘生丁合用卡介苗治疗。

(二)疗效机制研究

1. 用垂直传播感染鸭乙肝病毒(DHBV)阳性的麻鸭,分成三组,一组猪苓多糖 5mg/kg,每周 3 次,连续给药 3 个月。另一组注射猪苓多糖剂量用法同上,并注射乙肝疫苗 5 μ g/只,每 2 周 1 次,连续 3 次,连续 3 个月。对照组注射生理水 0.5ml/kg,每周 3 次,连续 3 个月。结果见表 4,提示猪苓多糖加乙肝疫苗组与猪苓多糖单用组均有抑制 DHBV 复制和改善肝脏病变的作用,尤以前者作用更强。

Table 4 Therapeutic effect on DHBV

group	end of therapy	2weeks after therapy	liver lesion
A	6/9	7/9	+
B	5/10	5/10	++
C	1/9	1/9	+++

A: polysaccharide of polyporus umbellatus + HBV vaccine

B: polysaccharide of polyporus umbellatus

C: control

给 DHBV(+) 麻鸭注射猪苓多糖 30mg/kg 和乙肝疫苗 15μg/kg, 每周 3 次, 连续 3 个月。除有明显抑制 DHBV 复制及改善肝脏病变作用外, 并取鸭肝提取 DHBV DNA 作 Southern blot, 发现治疗的 10 只麻鸭均有松环(Relaxed circular)DHBV DNA 的消失, 可能与猪苓多糖合用乙肝疫苗抑制 HBV DNA 逆转录过程有关。

但应用潘生丁合用卡介苗治疗 DHBV(+) 麻鸭, 血 DHBVDNA 阴转率为 5/10, 而单用潘生丁为 1/10。结果提示潘生丁合用卡介苗对 DHBV 复制有抑制作用, 但单用潘生丁抑制作用不明显, 二组均无明显改善肝脏病变的作用。

2. 用猪苓多糖、乙股疫苗、潘生丁和卡介苗单独和联合给小鼠腹腔注射, 取腹腔巨噬细胞测定其吞噬功能和细胞溶解功能, 发现单用猪苓多糖或分别与其它三种药物合用均可增强小鼠腹腔巨噬功能和细胞溶解功能。但其它三种药物单用, 小鼠腹腔巨噬细胞的吞噬和细胞溶解功能均无明显增强作用。

3. 对猪苓多糖、乙肝疫苗和卡介苗体外对正常人外周血单个细胞(PBMC)杀伤活性影响研究。结果表明猪苓多糖、卡介苗均可明显增强 PBMC 对 2.2.15 细胞、HepG2 细胞和 K562 细胞的杀伤活性, 并呈剂量依赖性。但乙肝疫苗对正常人 PBMC 的杀伤活性无增强作用, 与猪苓多糖联合诱导 PBMC 后其杀伤活性亦不比单作猪苓多糖高。

用猪苓多糖和卡介苗诱导 PBMC 的同时, PBMC 细胞膜上的 IL-2 受体(IL-2 R)表达明显增强, 还能促进 IL-2 的分泌, 并呈剂量依赖性, 上述研究证明猪苓多糖和卡介苗可能是通过促进免疫活性细胞分泌 IL-2 和增强 IL-2R 的表达而增强其杀伤活性。

对 30 例用 LAK 细胞回输治疗的乙型慢性活动性肝炎的男性病人、进行治疗前、后 LAK 细胞活性及血清 LAK 活性抑制因子测定, 以治疗结束时 HBV DNA 阴转作为治疗有效的考核指标, 发现治疗前 LAK 细胞活性, 治疗后 LAK 细胞活性是否升高及血清 LAK 活性抑制因子抑制率的高低, 均与 HBV DNA 阴转与否无明显关系, 根据目前研究, 测定 LAK 细胞活性和血清 LAK 活性抑制因子, 还不能作为预测 LAK 细胞回输治疗是否有效的指标。

二、重症肝炎部分

(一)重症肝炎的临床验证和疗效考核 结果见表 5、6、7。

Table 5 Therapeutic effect on severe hepatitis

group	total	mortality(%)
PHGF	80	31 (38.8) #
PGE1	24	9 (37.5) #
PHGF + PGE1	1	1
control	61	40 (65.8)
(basic therapy)		
total	166	81 (48.8)

compared with control P<0.05

Table 6 Therapeutic effect on severe hepatitis with coma

group	total	mortality(%)
PHGF	56	30 (53.6) #
PGE1	17	8 (47.1) #
control (basic therapy)	48	38 (79.2)
total	122	76 (62.8)

compared with control $P < 0.05$

Table 7 Effect of treatment in chronic hepatitis group and severe hepatitis group with cross-over design

group	No. of patients	No. of death	mortality rate(%)	
chronic hepatitis group	75	40	53.3	$P \geq 0.05$
severe hepatitis group	91	41	45.1	

HGF 组和 PGE1 组对重症肝炎或伴有 II⁰ 或 II⁰ 以上肝性脑病的重症肝炎的病死率均低于综合治疗组。经“慢肝组”和“重肝组”交叉验证重症肝炎的疗效,二组无明显差异,提示经多中心验证,结果可以重复。同时,对比“七五”和“八五”期间,用 HGF 和 PGE1 治疗重症肝炎病人,疗效无明显差异。HGF 治疗伴有 II⁰ 或 II⁰ 以上肝性脑病的重症肝炎病人,“七五”和“八五”期间疗效亦可无明显差异。提示综合治疗基础上加用 HGF 或 PGE1 对重症肝炎的疗效,在不同时期内可以重复。

副作用:一般 PHGF 无明显副作用,个别病人可出现低热和皮疹。但 PGE1 的副作用较大,部分病人可出现高热、恶心、呕吐、腹胀及低血压等,因副作用较大而不能继续治疗。

根据以上结果,我们认为对重症肝炎或伴有 II⁰ 或 II⁰ 以上肝性脑病的病人,首选在综合治疗基础上加用 PHGF 治疗。亦可在综合治疗基础上加 PGE1 治疗,但应注意其副作用。

(二)疗效机制研究

1. 各协作单位为了研究 PHGF 和 PGE1 对重症肝炎的疗效及其疗效机理,先后建立了应用大肠杆菌内毒素和鸭肝炎病毒(DHBV)联合诱发鸭急性肝坏死模型,D-氨基半乳糖和内毒素诱发小鼠暴发性肝炎模型和丙酸杆菌及内毒素诱发小鼠肝坏死等多种动物肝坏死模型,为深入研究 PHGF 和 PGE1 对肝坏死的治疗作用及其疗效机理提供可靠和实用的动物模型。

2. 采用大肠杆菌内毒素和 DHBV 联合诱导鸭急性肝坏死模型,在注射内毒素及 DHBV 后 2 小时,用 PHGF10mg 加入 5% 葡萄糖液中,静脉滴注,并静脉滴注白蛋白和 5% 葡萄糖液作对照。结果显示,注射 PHGF 组血清过氧化脂质(LPO)水平较对照组明显降低,肝脏炎症坏死及变性病变明显减轻,电镜检查显示内质网和线粒体病变也有明显改善。提示 PHGF 不仅能促进肝细胞再生和修复,还能降低肝坏死时血清 LPO 水平,减少细胞膜脂质过氧化,稳定细胞膜,减轻肝细胞损伤。

3. 采用 D-氨基半乳糖胺和内毒素联合诱导,建立小鼠暴发性肝炎模型,研究了 PGE1 和 PHGF 的治疗效果和对血清肿瘤坏死因子(STNF)的影响。结果显示 24 小时小鼠死亡率,PGE1 组和 PHGF 组分别为 36.4% 及 35.3%,对照组为 64.8%, $P < 0.05$ 。同时,检测 STNF 水平,PHGF 组和 PGE1 组均有